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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/763,276	01/26/2004	Masabumi Shibuya	249-323	6571

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EXAMINER	
REDDIG, PETER J	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 08/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/763,276	SHIBUYA ET AL.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *May 30, 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,10,43 and 44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,10,43 and 44* is/are rejected.

7)☒ Claim(s) *10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/17/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed on May 30, 2006 in response to the Office Action of December 30, 2005 is acknowledged and has been entered.

Claims 1, 2, 10, 43, 44 are pending.

Claims 1, 2, 10, 43, 44 are currently under consideration.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

3. The following grounds of rejection are maintained.

4. Claims 1, 2, and 10 remain rejected and new claims 43 and 44 are rejected under 35 USC112, first paragraph for the reasons previously set forth in the paper mailed December 30, 2005, pages 3-5

Applicant argues that the submitted declaration demonstrating that the cell growth of endothelial cells is inhibited by contacting vascular cells with the anti-py1175 antibody and that since the antibody of the present invention can inhibit cell growth of endothelial cells, the disclosure is enabling.

The argument has been considered but has not been found persuasive because the Declaration submitted under 37 C.F.R. 132 require that the antibody be injected into the cell or transfected into the cell to achieve the observed effects. These techniques are not applicable for *in vivo*/therapeutic use in which the antibody must be able to contact antigen presented on the surface of the cell. Furthermore, given the teachings of Jain et al and Weimer et al as previously set forth, it could not be predicted, nor would it be expected, based on the information in the

specification as originally filed and that in the declaration instantly presented that the invention will function as claimed for the reasons of record.

Applicant argues that Example 5 enables the claimed invention. The argument has been considered but has not been found persuasive because, like the data presented in the Declaration, the cell studies are done with cells that have been processed in such as way as to facilitate internalization of the antibodies – that is, they are "transparent" to the antibodies and for the reasons of record, the claimed invention is not enabled.

New Claim Objections

Claim 10 is objected to because of the following informalities: It appears that the applicant has made an inadvertent typographical error in claiming KDR/Flt -1, where it is clear applicant intended to be KDR/FlK-1. Given the teaching in the specification and the claims as constituted, it will be assumed for examination purposes that claim 10 is meant to be drawn to KDR/FlK-1

Appropriate correction is required.

New Grounds of Rejection

4. The specification is objected to AND claims 43 and 44 are rejected under 35 U.S.C. § 112, first paragraph, for failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are known and readily available to the public.

The claims are drawn to a monoclonal antibody produced by hybridoma KM3035 (FERM BP-7729).

It is unclear if a cell line that produces an antibody having the exact structural and chemical identity of monoclonal antibody FERM BP-7729 is known and publicly available, or can be reproducibly isolated without undue experimentation. Clearly, without access to the hybridoma cell lines producing said monoclonal antibody, it would not be possible to practice the claimed invention. Therefore, suitable deposits for patent purposes are required. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

It is noted that Applicants have deposited the hybridoma KM3035 as FERM BP-7729 (para.0216) in the International Patent Organism Depositary, National Institute of Advanced Industrial Science and Technology (AIST Tsukuba Central 6, 1-1, Higashi 1-Chome Tsukuba-shi, Ibaraki-ken 305-8566 Japan), but there is no indication in the specification as to public availability.

If a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will

be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications. Applicant's provision of these assurances would obviate this objection/rejection.

Affidavits and declarations, such as those under 37 C.F.R. § 1.131 and 37 C.F.R. § 1.132, filed during prosecution of the parent application do not automatically become a part of this application. Where it is desired to rely on an earlier filed affidavit, the applicant should make the remarks of record in the later application and include a copy of the original affidavit filed in the parent application

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

5. If the applicant were able to overcome the rejections set forth above, claims 1, 2, 10, 43 and 44 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification,

while being enabling for a method for inhibiting KDR/FLk-1 signal transduction in endothelial cells or inhibiting cell growth of endothelial cells, which comprise contacting the cells with a monoclonal antibody which specifically recognizes 1175-tyrosine phosphorylated KDR/FLk-1 or **antigen binding** fragment thereof, wherein the monoclonal antibody inhibits binding of phospholipase C-γ to 1175-tyrosine phosphorylated KDR/Flk-1, wherein the monoclonal antibody is a humanized anti-1175 tyrosine phosphorylated KDR/Flk-1 antibody, and wherein the humanized anti-1175-tyrosie phosphorylated KDR/Flk1 antibody is a human chimeric antibody or a human complementarity-deterimining region (CDR)-grafted antibody, does not reasonably provide enablement for a method for inhibiting KDR/FLk-1 signal transduction in endothelial cells or inhibiting cell growth of endothelial cells, which comprise contacting the cells with a monoclonal antibody which specifically recognizes 1175-tyrosine phosphorylated KDR/FLk-1 or an **antibody fragment thereof**, wherein the monoclonal antibody inhibits binding of phospholipase C-γ to 1175-tyrosine phosphorylated KDR/Flk-1, wherein the monoclonal antibody is a humanized anti-1175 tyrosine phosphorylated KDR/Flk-1 antibody, and wherein the humanized anti-1175-tyrosie phosphorylated KDR/Flk1 antibody is a human chimeric antibody or a human complementarity-deterimining region (CDR)-grafted antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to a method for inhibiting KDR/FLk-1 signal transduction in endothelial cells or inhibiting cell growth of endothelial cells, which comprise contacting the cells with a monoclonal antibody which specifically recognizes 1175-tyrosine phosphorylated

KDR/FLk-1 or antibody fragment thereof, wherein the monoclonal antibody inhibits binding of phospholipase C-γ to 1175-tyrosine phosphorylated KDR/Flk-1, wherein the monoclonal antibody is a humanized anti-1175 tyrosine phosphorylated KDR/Flk-1 antibody, and wherein the humanizedanti-1175-tyrosie phosphorylated KDR/Flk1 antibody is a human chimeric antibody or a human complementarity-deterimining region (CDR)-grafted antibody.

This means that the claims encompass the use of the monoclonal antibody to 1175 tyrosine phosphorylated KDR/Flk-1 and antibody fragment, including fragments that do not bind to the antigen, as a therapeutic antibody.

The specification teaches that angiogenesis is important in various diseases such as tumorigenesis, diabetic retinopathy, and rheumatoid arthritis, see para 0005.

The specification teaches that Flt-1 and KDR/Flk-1 are membrane proteins of 180 to 200 kDa in molecular weight belonging to the receptor tyrosine kinase family which have 7 immunoglobulin-like domains as an extracellular domain and a tyrosine kinase domain as an intracellular domain.

The specification teaches that vascular endothelial cell growth factor (VEGF) specifically binds to KDR/Flk-1 at KD value of 75 pmol/l and that KDR/Flk-1 is specifically expressed in vascular endothelial cells, see para 0009.

The specification further teaches that KDR/Flk-1 relates to the growth and migration of vascular endothelial cells among various activities of VEGF. The specification hypothesizes that since growth and blood vessel formation were not found and blood island of yolk sac was not formed in knockout mice in which the KDR/Flk-1 gene had been destroyed, and they died at a

fetal stage of days 8.5 to 9.5 after development, KDR/Flk-1 relates to the growth and differentiation of vascular endothelial cells in an animal, see para 0011.

The specification teaches that KDR/Flk-1 is activated and auto-phosphorylated by VEGF stimulation, PLC-γ binds to the KDR/Flk-1 and is then activated by phosphorylation, PKC is subsequently activated, and as a result MAP kinase is activated and DNA synthesis is induced. The specification teaches that phosphorylation of 1175-tyrosine participates in the phosphorylation of PLC-γ and activation of MAP kinase by expressing a mutant of KDR/Flk-1, in which 1175- and 1214-tyrosine residues are replaced by phenylalanine residues, in a cell line derived from endothelial cells, para 0015.

The specification teaches that the monoclonal antibody was prepared using a peptide peptide which comprises an amino acid sequence of 5 to 20 residues containing the 1175-tyrosine in the amino acid sequence of KDR/Flk-1 shown in SEQ ID NO: 7, wherein the amino acid corresponds to the 1175-tyrosine is a phosphorylated tyrosine, see para. 0115.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are drawn to antibody therapeutics using an antibody fragment. This encompasses using fragments of the antibody that do not bind to the antigen of interest. This would lead to insufficient target specificity, as discussed by Weiner (Seminars in Oncology, 1999, 26:41-50) as a problem of antibody therapy. Thus, one of skill of in the art would not predictably expect an antibody fragment that does not have the ability to bind with KDR/Flk-1 phosphorylated at tyrosine 1175 to have the same effect of the claimed monoclonal antibody which specifically recognizes 1175 tyrosine phosphorylated KDR/Flk-1 or an antigen binding

fragment thereof. Thus undue experimentation would be required to practice the invention as claimed.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated with a reasonable expectation of success. For the above reasons, it appear that undue experimentation would be required to practice the claimed invention.

6. All other rejections recited in the previous office action are hereby withdrawn.

7. Applicant's amendment necessitated the new grounds of rejection. Thus, **THIS ACTION IS MADE FINAL.** *Applicant is reminded of the extension of time policy as set forth in* 37 C.F.R. 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Peter J. Reddig, Ph.D.
Examiner
Art Unit 1642

PJR

SUSAN UNGAR, PH.D
PRIMARY EXAMINER